

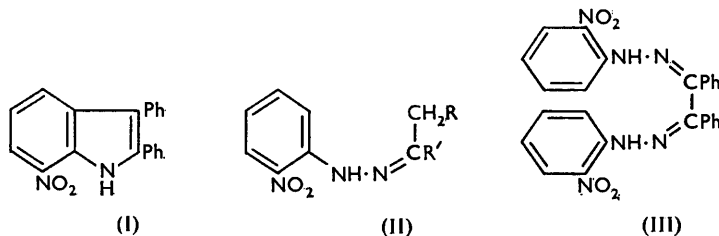
### 940. The Formation of Osazones during Attempted Fischer Indole Syntheses.

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Treatment of deoxybenzoin *o*-nitrophenylhydrazone with *o*-nitrophenylhydrazine in acid solution leads to benzil di-*o*-nitrophenylhydrazone. The mechanism of this reaction is discussed. The behaviour of certain other *o*-nitrophenylhydrazones under the conditions of the Fischer indole synthesis has been investigated.

DURING attempts to prepare 7-nitro-2:3-diphenylindole (I) by a Fischer synthesis, deoxybenzoin *o*-nitrophenylhydrazone (II; R = R' = Ph) was heated with acetic and hydrochloric acid. The product, however, was not the indole (I) but was identified as benzil di-*o*-nitrophenylhydrazone (III) which was synthesised from benzil and *o*-nitrophenylhydrazine.

It seemed likely that this osazone (III) was formed by reaction between the hydrazone (II; R = R' = Ph) and free *o*-nitrophenylhydrazine obtained from it by hydrolysis since, when *o*-nitrophenylhydrazine was added to the boiling mixture of the hydrazone (II; R = R' = Ph) and acetic and hydrochloric acids, the yield of the osazone was increased.



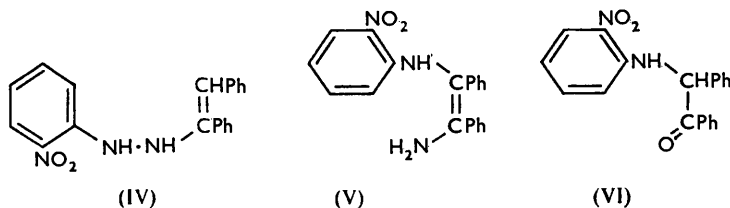
Further, *o*-nitroaniline was isolated from the mother-liquors of the reaction. This suggested that the oxidation of deoxybenzoin *o*-nitrophenylhydrazone to a derivative of benzil involved the corresponding reduction of *o*-nitrophenylhydrazine to *o*-nitroaniline, as occurs during the formation of the osazones of sugars.<sup>1,2</sup> A probable mechanism (suggested to the authors by Dr. M. J. T. Robinson) is that the tautomeric form (IV) of the hydrazone (II; R = R' = Ph) is first converted into the vinylamine (V) by a rearrangement which is related to an *o*-semidine rearrangement<sup>3</sup> in the same way that the first stage

<sup>1</sup> Percival, "Advances in Carbohydrate Chemistry," Academic Press Inc., New York, 1948, Vol. III, p. 23.

<sup>2</sup> Braude and Forbes, *J.*, 1951, 1762.

<sup>3</sup> Cf. Hughes and Ingold, *Quart. Reviews*, 1952, 6, 34.

of the accepted mechanism of the Fischer indole synthesis<sup>4,5</sup> is related to an *o*-benzidine rearrangement. Hydrolysis of the vinylamine (V) would give the desylamine (VI) from which benzil di-*o*-nitrophenylhydrazone would be obtained by reaction with *o*-nitrophenylhydrazine,<sup>6</sup> either directly or by the prior formation of benzoin by further hydrolysis. In these later reactions, *o*-nitrophenylhydrazine would be reduced to *o*-nitroaniline, possibly



by the mechanism for osazone formation suggested by Braude and Forbes.<sup>2</sup> Robinson and Robinson<sup>4</sup> have previously pointed out that *o*-semidine rearrangements could occur during indole syntheses, and Dalglish and Mann<sup>7</sup> have observed the inhibiting effect of an *ortho*-substituent on certain Fischer indole reactions.

The experiments described above suggested that *o*-nitrophenylhydrazones resistant to the Fischer synthesis might give osazones under similar conditions. This was found to be the case with acenaphthenone *o*-nitrophenylhydrazone which was known not to undergo cyclisation to an indole<sup>8</sup> and, when acenaphthenone was heated with *o*-nitrophenylhydrazine and acetic and hydrochloric acid, acenaphthenequinone di-*o*-nitrophenylhydrazone was obtained.

Contrary to previous experience,<sup>9</sup> coumaranone *o*-nitrophenylhydrazone was readily converted into the corresponding indole.

It was found that, while indan-2-one *o*-nitrophenylhydrazone cyclised to 7-nitroindeno-(2' : 3'-2 : 3)indole, the *o*-nitrophenylhydrazones of indan-1-one and propiophenone gave neither the indole nor the osazone. Further, Schofield and Theobald<sup>10</sup> have made 2-methyl-7-nitro-3-phenylindole from benzyl methyl ketone *o*-nitrophenylhydrazone. Now, since by the Fischer synthesis the *o*-nitrophenylhydrazones of simple aliphatic and alicyclic ketones readily provide 7-nitroindoles,<sup>11</sup> these results suggest that the indolisation of an *o*-nitrophenylhydrazone (II; R = alkyl or aryl) will occur if R' is aliphatic, but will not proceed if R' is aromatic. The example of coumaranone *o*-nitrophenylhydrazone shows, however, that this is not invariably the case.

In the reaction between 9-phenanthrol and *o*-nitrophenylhydrazine in acetic and hydrochloric acid, both indolisation and oxidation took place, leading to the formation of a mixture of 7'-nitroindolo(2' : 3'-9 : 10)phenanthrene and phenanthraquinone *o*-nitrophenylhydrazone, *o*-nitroaniline being obtained at the same time. Since 9-phenanthrol is known to undergo aerial oxidation to phenanthraquinone,<sup>12</sup> it is possible that some oxidation occurred in this way during this reaction with *o*-nitrophenylhydrazine.

#### EXPERIMENTAL

*Benzil Di-o-nitrophenylhydrazone.*—(a) Deoxybenzoin *o*-nitrophenylhydrazone<sup>13</sup> (1.1 g.), *o*-nitrophenylhydrazine (1.5 g.), acetic acid (20 c.c.), and concentrated hydrochloric acid (10 c.c.) were refluxed together for 1½ hr., and the precipitate (0.7 g., 44%) of *benzil di-o-nitrophenylhydrazone* was collected and washed with acetic acid. It crystallised from anisole in red needles,

<sup>4</sup> Robinson and Robinson, *J.*, 1918, **113**, 639.

<sup>5</sup> Allen and Wilson, *J. Amer. Chem. Soc.*, 1943, **65**, 611.

<sup>6</sup> Cf. Wolf, *Chem. Ber.*, 1953, **86**, 840.

<sup>7</sup> Dalglish and Mann, *J.*, 1947, 653.

<sup>8</sup> Bannister and Plant, *J.*, 1948, 1247.

<sup>9</sup> Cawley and Plant, *J.*, 1938, 1214.

<sup>10</sup> Schofield and Theobald, *J.*, 1950, 1505.

<sup>11</sup> Perkin and Riley, *J.*, 1923, **123**, 2399; Plant, *J.*, 1929, 2493; Bauer and Strauss, *Ber.*, 1932, **65**, 308; Hughes, Lions, and Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1938, **72**, 209.

<sup>12</sup> Japp and Findlay, *J.*, 1897, **71**, 1115.

<sup>13</sup> Fennell and Plant, *J.*, 1932, 2872.

m. p. 260—263°, not depressed by admixture with an authentic sample (see below) (Found : C, 65.1; H, 4.5.  $C_{26}H_{20}O_4N_6$  requires C, 65.0; H, 4.2%). The acid filtrates from the Fischer reaction were diluted with water (150 c.c.), rendered alkaline with sodium hydroxide (40 g.), and, after addition of sodium sulphate (10 g.), were steam-distilled until the distillate, at first yellow, was colourless. From the latter (1200 c.c.) *o*-nitroaniline (0.4 g.), m. p. 71—73°, identified by mixed m. p., was isolated with ether.

(b) Benzil (0.7 g.) and *o*-nitrophenylhydrazine (1 g.) were heated together at 150° for  $\frac{1}{2}$  hr. The solid was washed with acetic acid and crystallised first from benzene and then from anisole, to give red needles, m. p. 261—263°, of benzil di-*o*-nitrophenylhydrazone (Found : C, 65.0; H, 4.4; N, 17.3.  $C_{28}H_{20}O_4N_6$  requires C, 65.0; H, 4.2; N, 17.5%), identical with the above.

The compound, m. p. 137°, reported by Guha and De<sup>14</sup> as benzil di-*o*-nitrophenylhydrazone is possibly the mono-*o*-nitrophenylhydrazone, as it was formed by heating equimolecular proportions of benzil and *o*-nitrophenylhydrazine in acetic acid, but attempts to repeat the preparation led to crude material, m. p. 125—130°, which could not be purified.

*Acenaphthenequinone Di-o-nitrophenylhydrazone.*—(a) Acenaphthenone (1 g.), *o*-nitrophenylhydrazine (3 g.), acetic acid (100 c.c.), and concentrated hydrochloric acid (20 c.c.) were refluxed together for  $3\frac{1}{2}$  hr. The precipitate crystallised from anisole, giving crimson microcrystalline *acenaphthenequinone di-o-nitrophenylhydrazone* (0.7 g.), m. p. 297—300° (decomp.), raised to 299—301° by further crystallisation from anisole, and not depressed by admixture with an authentic sample (see below) (Found : C, 63.9; H, 3.7.  $C_{24}H_{16}O_4N_6$  requires C, 63.7; H, 3.5%).

(b) Acenaphthenequinone<sup>15</sup> (0.9 g.) and *o*-nitrophenylhydrazine (1.5 g.) were heated together for 50 min. at 140°. The solid crystallised from anisole as crimson, microcrystalline needles (0.9 g.), m. p. 299—301° (decomp.), of *acenaphthenequinone di-o-nitrophenylhydrazone*.

*7-Nitrocoumarono(3' : 2'-2 : 3)indole.*—Coumaranone *o*-nitrophenylhydrazone<sup>9</sup> (1 g.) was refluxed with acetic acid (9 c.c.) and concentrated hydrochloric acid (5 c.c.) for 40 min. The product (0.5 g.) was collected and crystallised from acetic acid, giving the *indole* as red needles, m. p. 248—251° (Found : C, 67.0; H, 3.3.  $C_{14}H_8O_3N_2$  requires C, 66.7; H, 3.2%).

*o-Nitrophenylhydrazones.*—Indan-2-one (0.6 g.) and *o*-nitrophenylhydrazine (0.7 g.) were heated together for 15 min. at 120°. Crystallisation from benzene gave *indan-2-one o-nitrophenylhydrazone* (0.7 g.) as orange needles, m. p. 173—176°, which became brown in air (Found : C, 67.1; H, 4.8.  $C_{15}H_{13}O_2N_2$  requires C, 67.4; H, 4.9%). Prepared in a similar way, *indan-1-one o-nitrophenylhydrazone* separated from benzene in red needles, m. p. 212—214° (Found : C, 67.8; H, 5.0%).

*7-Nitroindeno(2' : 3'-2 : 3)indole.*—After *indan-2-one o-nitrophenylhydrazone* (0.6 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (6 c.c.) had been refluxed together for  $1\frac{1}{2}$  hr., the solid (0.2 g.) which crystallised was purified by passing it, in benzene, through a short column of alumina. The product, obtained by evaporation, separated first from anisole and then from benzene, giving the *indole* as red needles, m. p. 234—237° (Found : C, 71.5; H, 4.0.  $C_{15}H_{10}O_2N_2$  requires C, 72.0; H, 4.0%).

*7'-Nitroindolo(2' : 3'-9 : 10)phenanthrene.*—9-Phenanthrol<sup>16</sup> (7 g.), *o*-nitrophenylhydrazine (15 g.), acetic acid (130 c.c.), and concentrated hydrochloric acid (100 c.c.) were boiled together under reflux for 3 hr. The precipitate was separated from the acid filtrates, washed with hot water, and dried. This crude mixture (8.5 g.; m. p. 205—213°) was crystallised twice from large quantities of ethyl acetate, and then from pyridine to give *phenanthraquinone o-nitrophenylhydrazone* (1.3 g.) as red needles, m. p. 247—249°, identical (mixed m. p.) with an authentic sample (see below). The mother-liquors from these crystallisations were evaporated and a portion (1.75 g.) of the residue, dissolved in benzene (1 l.), was passed through alumina (200 g.). Elution with benzene caused separation into an upper red band and a lower orange one. The latter was removed with benzene (6 l.), *7'-nitroindolo(2' : 3'-9 : 10)phenanthrene* (0.9 g.), m. p. 255—257°, being obtained by evaporation. It separated from pyridine in orange needles, m. p. 258—260° (Found : C, 77.1; H, 3.9; N, 8.7.  $C_{20}H_{15}O_2N_2$  requires C, 76.9; H, 3.8; N, 9.0%). Elution of the remaining red band with ethanol-benzene provided impure *phenanthraquinone o-nitrophenylhydrazone*.

*o*-Nitroaniline (0.8 g.; m. p. 69—72°) was isolated from the acid filtrates in the manner described above.

Phenanthraquinone *o*-nitrophenylhydrazone<sup>14</sup> was prepared by treating phenanthraquinone

<sup>14</sup> Guha and De, *J. Indian Chem. Soc.*, 1926, **3**, 41.

<sup>15</sup> *Org. Synth.*, 1944, **24**, 1.

<sup>16</sup> Fieser, Jacobsen, and Price, *J. Amer. Chem. Soc.*, 1936, **58**, 2163.

(0.4 g.) in boiling acetic acid (10 c.c.) with *o*-nitrophenylhydrazine (0.3 g.). The product (0.5 g.) separated immediately and crystallised from pyridine in red needles, m. p. 246—249° (Found: C, 69.8; H, 4.0; N, 12.3. Calc. for  $C_{20}H_{13}O_3N_3$ : C, 70.0; H, 3.8; N, 12.3%).

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